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3-Substituted 1,4-Benzodiazepin-2-ones

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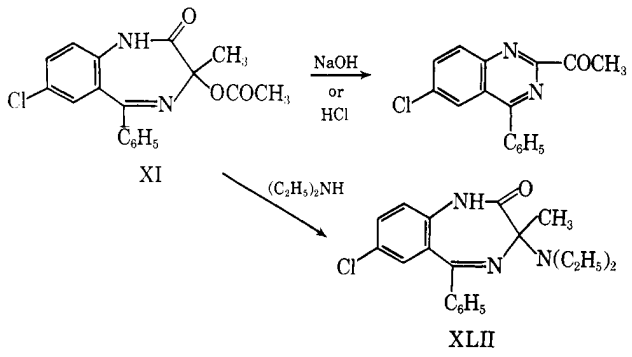
The preparation of a number of 1,4-benzodiazepines substituted in the 3 position is described. The rearrangement of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide with diacetyl sulfide yields largely the 3-acetylthio compound. Amines, ethers, and sulfides were prepared through the chloro intermediate. A 3-carbethoxybenzodiazepine was prepared and converted into oxazepam. The pharmacological test data of new and previously published compounds are given.

The possession of depressant activity in the central nervous system is a common property of 1,4-benzodiazepin-2-ones despite diverse substitution.[2] We have devoted most of our work with this system to 3-substituted benzodiazepines as exemplified by oxazepam (I) and report here syntheses of further compounds and biological test data of significance in this area.

In addition to the hydroxy group, halogens, ethers, amines, and variously substituted esters have been introduced into the 3 position. The new compounds have been prepared by the methods cited in Table I or as discussed below.

3-Acetoxy-7-chloro-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (XI) was obtained as expected upon treatment of 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide[3] with acetic anhydride, but attempted hydrolysis to the 3-hydroxy analog using strong base or acid resulted in a facile rearrangement to 2-acetyl-6-chloro-4-phenylquinazoline (Scheme I). A similar rearrangement in acid of the more stable I has been described.[4] Milder treatment of XI with diethylamine caused neither rearrangement nor hydrolysis but resulted in displacement of the acetoxy group to yield 7-chloro-3-diethylamino-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (XLII).

Scheme I



XLII

7-Chloro-5-*o*-chlorophenyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one 4-oxide and related compounds have been reported to undergo a Polonovski reaction upon treatment with diacetyl sulfide to afford 3-acetoxy-7-chloro-5-*o*-chlorophenyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one.[5] We have found, however, that treatment of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide with diacetyl sulfide gives a mixture of the 3-acetoxy (VII) and the 3-acetylthio (XXXIV) compounds with the latter predominating. The presence of thioacetic acid greatly increased the proportion of XXXIV (Scheme II). It was also found possible to replace the acetoxy group of VII by the acetylthio group to afford XXXIV by heating with thioacetic acid. In consonance with its mild acetylating power, thioacetic acid alone caused rearrangement of the 4-oxide and yielded XXXIV.

3-Halobenzodiazepin-2-ones were principally employed as intermediates in the production of 3-amines, 3-ethers, and 3-sulfides and the displacements proceeded unexceptionally.

The 3-carbethoxy compound LIII was prepared directly from 2-amino-5-chlorobenzophenone and aminomalonic ester.[6] Compound LIII was readily brominated in the 3 position and the resulting labile substituent was easily displaced by hydroxy and methoxy groups to afford LIV and LV (Scheme III). The benzodiazepine ring of LIV was unstable when treated with base. In contrast, LV was hydrolyzed by base and the product was decarboxylated upon acidification to give the 3-methoxybenzodiazepine XXII. Compound XXII was converted into I by reaction with boron tribromide followed by treatment with water.

Pharmacological Activity.—Results from two behavioral observation tests and three antagonism tests are recorded in Table I. The dose causing a motor activity decrease affords an estimate of the quieting effect and the dose producing ataxia is not only a measure of an undesirable side effect but may also give an indication of muscle relaxation. The antimorphine test detects both major and minor tranquilizers. The antipentylenetetrazole and antielectroshock tests are usually considered to be anticonvulsant tests. We have found the antipentylenetetrazole test particularly useful in forecasting responses to benzodiazepines in more sophisticated behavioral studies. A more detailed description of these tests has been given by Gluckman.[7]

The general requirements for good activity in the 1,4-benzodiazepines are with few exceptions met in the base structures employed here for study of the effects of varying substitution in the 3 position. Except for

(1) (a) Medicinal Chemistry Section. (b) Pharmacology Section.

(2) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).

(3) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

(4) S. C. Bell and S. J. Childress, *ibid.*, **29**, 506 (1964).

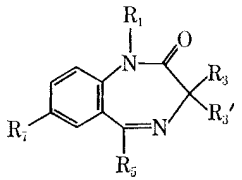
(5) E. Reeder, A. Stempel, and L. H. Sternbach, U. S. Patent 3,340,253 (1967).

(6) *Cf.* J. Schmitt, South African Patent 65/3049 (1966); Derwent Farmdoc 19574.

(7) M. I. Gluckman, *Current Therap. Res., Clin. Exptl.*, **7**, 721 (1965).

TABLE I

3-SUBSTITUTED 1,4-BENZODIAZEPIN-2-ONES



No.	R_1	R_3	R_3'	R_5	R_7	Mp, °C	Method[b]	Formula	Analyses	Biological activity (mice), mg/kg oral[a] Motor act. decrease MED[c]	Anti-pentylene-tetrazole ED_{50}	Antimax elec shock ED_{50}	Anti-morphine ED_{50}	Ataxia at 1 hr ED_{50}
I	H	OH	H	C_6H_5	Cl		A	$C_{15}H_{11}ClN_2O_2$		1.6	0.6	3.1	2.2	5
II	CH_3	OH	H	C_6H_5	Cl		A	$C_{16}H_{13}ClN_2O_2$		1.3	0.7	2.6	1.5	5
III	H	OH	H	*o*-ClC_6H_4	Cl	166–168	*Cf.* A	$C_{15}H_{10}Cl_2N_2O_2$	C, H, Cl, N	0.1	0.07	2.0	0.2	16
IV	CH_3	OH	H	*o*-ClC_6H_4	Cl	205–207	*Cf.* A	$C_{16}H_{12}Cl_2N_2O_2$	C, H, Cl, N	0.4	0.09	2.4	0.2	33
V	*c*-$C_3H_5CH_2$	OH	H	C_6H_5	Cl	159–161	*Cf.* A	$C_{19}H_{17}ClN_2O_2$	C, H, Cl, N	0.4	6.2	13	5.8	11
VI	H	$OCOCH_3$	H	C_6H_5	H		A	$C_{17}H_{14}N_2O_3$		40	31	71	91	135
VII	H	$OCOCH_3$	H	C_6H_5	Cl		A	$C_{17}H_{13}ClN_2O_3$		1.6	2.6	3.8	7.5	7
VIII	CH_3	$OCOCH_3$	H	C_6H_5	Cl		A	$C_{18}H_{15}ClN_2O_3$		13	3.4	2.3	13	143
IX	*c*-$C_3H_5CH_2$	$OCOCH_3$	H	C_6H_5	Cl	194–196	*Cf.* A	$C_{21}H_{19}ClN_2O_3$	C, H, Cl, N	4.0	4.5	25	13	44
X	H	$OCOCH_3$	H	*o*-ClC_6H_4	Cl	260–262	*Cf.* A	$C_{17}H_{12}Cl_2N_2O_3$	C, H, N	1.0	0.3	3.7	0.1	30
XI	H	$OCOCH_3$	CH_3	C_6H_5	Cl	179–180	B	$C_{18}H_{15}ClN_2O_3$	C, H, Cl, N	>400	127		>127	
XII	H	$OCOC_6H_5$	H	C_6H_5	Cl		A	$C_{22}H_{15}ClN_2O_3$		6.3	1.2	>40	12	21
XIII	H	$OCOCH_2Cl$	H	C_6H_5	Cl		A	$C_{17}H_{12}Cl_2N_2O_3$		4.0	2.0	13	4.7	23
XIV	H	$OCOCH_2C_4H_8ON$[d]	H	C_6H_5	Cl		A	$C_{21}H_{20}ClN_3O_4$		1.3	0.8	7.5		8
XV	H	$OCOCH_2NC_5H_5Cl$[e]	H	C_6H_5	Cl	176–178	*Cf.* A	$C_{22}H_{17}Cl_2N_3O_3 \cdot H_2O$	C, H, Cl, N	0.4	0.8	8.2	3.6	10
XVI	H	$OCOCH_2CH_2C_5H_9$-*c*	H	C_6H_5	Cl	198–200	*Cf.* A	$C_{33}H_{23}ClN_2O_5$	C, H, Cl, N	400	30	127	80	340
XVII	H	$OCOCH_2CH_2CO_2H$	H	C_6H_5	Cl	110–112	B	$C_{19}H_{15}ClN_2O_5 \cdot H_2O$	C, H, Cl, N	4.0	1.1	17	2.2	16
XVIII	H	$OCOCH_2CH_2CO_2H$	H	*o*-ClC_6H_4	Cl	123–125	*Cf.* B	$C_{19}H_{14}Cl_2N_2O_5 \cdot C_2H_5OH \cdot 0.5H_2O$	C, H, Cl, N	1.3	0.05	5.7	1.3	10
XIX	$COCH_3$	$OCOCH_3$	H	C_6H_5	Cl		C	$C_{19}H_{15}ClN_2O_4$		4.0	0.9	4.8	5.8	16
XX	$COCH_3$	$OCOCH_3$	H	*o*-ClC_6H_4	Cl	171–173	*Cf.* C	$C_{19}H_{14}Cl_2N_2O_4$	C, H, Cl, N	1.3	0.4	2.3	0.2	27
XXI	$COCH_2Cl$	$OCOCH_3$	H	C_6H_5	Cl	195–197	B	$C_{19}H_{14}Cl_2N_2O_4$	C, H, N	40	6.0	40	33	110
XXII	H	OCH_3	H	C_6H_5	Cl	256–258	B	$C_{16}H_{13}ClN_2O_2$	C, H, Cl, N	13	6.0		3.9	
XXIII	CH_3	OCH_3	H	C_6H_5	Cl	145–146	*Cf.* B	$C_{17}H_{15}ClN_2O_2$	C, H, Cl	1.3	0.4	0.9	2.7	2
XXIV	H	OCH_3	H	*o*-ClC_6H_4	Cl	222–224	*Cf.* B	$C_{16}H_{12}Cl_2N_2O_2$	C, H, Cl, N	0.1	0.5	2.2	0.2	12
XXV	CH_3	OCH_3	H	*o*-ClC_6H_4	Cl	142–144	*Cf.* B	$C_{17}H_{14}Cl_2N_2O_2$	C, H, Cl	0.1	0.4	0.7	0.3	1
XXVI	H	OC_2H_5	H	C_6H_5	Cl		A	$C_{17}H_{15}ClN_2O_2$		25	5.7		21	56
XXVII	H	OC_2H_5	H	*o*-ClC_6H_4	Cl	181–183	*Cf.* B	$C_{17}H_{14}Cl_2N_2O_2$	C, H, Cl, N	0.4	0.5	2.6	1.5	10
XXVIII	H	$OCH_2CO_2C_2H_5$	H	C_6H_5	Cl	148–149	B	$C_{19}H_{17}ClN_2O_4$	C, H, Cl, N	40	>127		>127	
XXIX	H	OCH_2CO_2H	H	C_6H_5	Cl	205–207	B	$C_{17}H_{13}ClN_2O_4$	C, H, Cl, N	40	75	>40	>40	>40
XXX	H	Cl	H	C_6H_5	Cl		A	$C_{15}H_{10}Cl_2N_2O$		0.4	0.2	3.0	1.0	12
XXXI	H	Cl	H	*o*-ClC_6H_4	Cl	211–213	*Cf.* A	$C_{15}H_9Cl_3N_2O$	C, H, N	0.1	0.2	1.4	0.3	15
XXXII	CH_3	Cl	H	*o*-ClC_6H_4	Cl	215–217	*Cf.* A	$C_{16}H_{11}Cl_3N_2O$	C, H, N	0.4	0.2		1.4	
XXXIII	H	SH	H	C_6H_5	Cl	140–141	B	$C_{15}H_{11}ClN_2OS \cdot 0.5C_2H_5OH$	C, H, Cl, N	13	45	25	44	31
XXXIV	H	$SCOCH_3$	H	C_6H_5	Cl	208–209	B	$C_{17}H_{13}ClN_2O_2S$	C, H, Cl, N	40	13	100	40	250
XXXV	H	$SCH_2CH_2N(C_2H_5)_2$	H	C_6H_5	Cl	255–260	B	$C_{21}H_{24}ClN_3OS \cdot HCl$	H, N, S; C[f]	400	400		120	
XXXVI	H	SC_3H_4NS[b]	H	C_6H_5	Cl	213–215	B	$C_{18}H_{14}ClN_3OS_2$	C, H, Cl, N	400	>400		>400	
XXXVII	H	NH_2	H	C_6H_5	Cl		D	$C_{15}H_{12}ClN_3O$		40	7.8	13	21	68

XXXVIII	H	NH_2	H	o-ClC_6H_4	Cl	217–218	*Cf.* D	$C_{15}H_{11}Cl_2N_3O \cdot HCl \cdot H_2O$	C, H, Cl, N	40	3.0	3.5	3.5	46
XXXIX	H	$NHCH_3$	H	C_6H_5	Cl	227–230	*Cf.* B	$C_{16}H_{14}ClN_3O \cdot HCl \cdot C_2H_5OH$	C, H, Cl, N	400	>40	>40	S[g]	>40
XL	H	NC_4H_8O[d]	H	C_6H_5	Cl	211–213	*Cf.* B	$C_{19}H_{18}ClN_3O_2$	C, H, Cl, N	127	17	>400	56	
XLI	H	$NHCH_2CH_2N(CH_3)_2$	H	C_6H_5	Cl	182–183	B	$C_{19}H_{21}ClN_4O$	C, H, Cl, N	40	54	>400	68	
XLII	H	$N(C_2H_5)_2$	CH_3	C_6H_5	Cl	178–179	B	$C_{20}H_{22}ClN_3O$	C, H, Cl, N	127	>127	>127	>127	>127
XLIII	H	NC_5H_5Cl[e]	H	C_6H_5	Cl	250–251	B	$C_{20}H_{15}Cl_2N_3O$	C, H, Cl, N	40	>127		S	
XLIV	H	NHCHO	H	C_6H_5	Cl	243–245	*Cf.* D	$C_{16}H_{12}ClN_3O_2$	C, H, Cl, N	400	38	>127		
XLV	H	$NHCOCH_3$	H	C_6H_5	Cl		D	$C_{17}H_{14}ClN_3O_2$		127	500			
XLVI	H	$NHCOCH_3$	H	o-ClC_6H_4	Cl	286–287	*Cf.* D	$C_{17}H_{13}Cl_2N_3O_2$	C, H, N	>400	>400		90	
XLVII	H	$N(CH_3)COCH_3$	H	C_6H_5	Cl	265–267	*Cf.* D	$C_{18}H_{16}ClN_3O_2$	H, Cl, N; C[f]	>400	>400		>400	
XLVIII	H	$NHCOCH_2CH_2C_6H_5$	H	C_6H_5	Cl	230–232	*Cf.* D	$C_{24}H_{20}ClN_3O_2$	C, H, Cl, N	>400	>127		S	
XLIX	H	$NHCOC_6H_5$	H	C_6H_5	Cl	238–240	*Cf.* D	$C_{22}H_{16}ClN_3O_2$	C, H, Cl	>400	>40		>40	
L	H	$NHCOCH_3$	H	CH_3	H	231–233	*Cf.* D	$C_{12}H_{13}N_3O_2$	C, H, N	400	>127		>127	
LI	H	$NHCO_2C_2H_5$	H	C_6H_5	Cl		E	$C_{18}H_{16}ClN_3O_3$		>400	>400		>400	
LII	$CO_2C_2H_5$	$NHCO_2C_2H_5$	H	C_6H_5	Cl	190–192	B	$C_{21}H_{20}ClN_3O_5$	C, H, Cl	>400	>400		>400	
LIII	H	$CO_2C_2H_5$	H	C_6H_5	Cl	227–228	B	$C_{18}H_{15}ClN_2O_3$	C, H, Cl, N	4.0	2.4	13	11	38
LIV	H	$CO_2C_2H_5$	OH	C_6H_5	Cl	180–181.5	B	$C_{18}H_{15}ClN_2O_4$	C, H, Cl, N	127	6.2	86	37	110
LV	H	$CO_2C_2H_5$	OCH_3	C_6H_5	Cl	168–170	B	$C_{19}H_{17}ClN_2O_4$	C, H, Cl, N	13	40	>127	>127	>127
LVI	H	$CO_2C_2H_5$	OC_2H_5	C_6H_5	Cl	164–166	*Cf.* B	$C_{20}H_{19}ClN_2O_4 \cdot 0.5C_2H_5OH$	C, H, Cl, N	127	40	>40	>40	>40

[a] For descriptions of the biological tests see ref 2 and 7. [b] Methods of preparation are given in the citations excepting those wherein *Cf.* is employed. Preparations of closely analogous compounds are described in those instances. A: S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962); B: Experimental Section, this paper; C: S. C. Bell and P. H. L. Wei, *J. Org. Chem.*, **30**, 3576 (1965); D: S. C. Bell, R. J. McCaully, and S. J. Childress, *ibid.*, **33**, 216 (1968); E: S. C. Bell, *ibid.*, **33**, 828 (1968). [c] MED = minimal effective dose. [d] C_4H_8ON = morpholino. [e] NC_5H_5Cl = pyridinium chloride. [f] *Anal.* C: calcd, 57.53; found, 57.02. [g] S = synergistic. [h] SC_3H_4NS = 2-thiothiazoline. [i] *Anal.* C: calcd, 63.31; found, 62.79.

VI and L all of the compounds have a 7-chloro substituent and carry a phenyl or *o*-chlorophenyl substituent at the 5 position. Most of the compounds are unsubstituted in the 1 position. By comparing the data for unalkylated and 1-alkylated pairs, *e.g.*, I and II, it can be seen that no tremendous difference arises in the antagonism tests by alkylation. It should be noted, however, that 1-methylation does result in considerable muscle relaxant activity as measured by suppression of the linguomandibular reflex in cats.[7] Compounds II and IV have, respectively, twentyfold and twice the potency of their unmethylated analogs, I (ED_{50} = 4.2 mg/kg) and III (ED_{50} = 0.65 mg/kg), in this test. Acyl groups in the 1 position also appear to have little effect, possibly because of ready hydrolysis *in vivo*.

Turning to the varying 3 substituents it can be seen that the usual pattern of benzodiazepine activity is preserved; that is, a compound active in one of these tests is active in all. There are, however, quantitative differences; the most potent compound in one test is not necessarily the most potent in the others.

Placement of a hydroxyl group in the 3 position results in compounds (I–V) having the highest potency in the antipentylenetetrazole test, which can be considered as representative of the total effect. The comparisons that follow are based on this test. Although acylation of the 3-hydroxy group (VI–XXI) lowers potency there is reason to believe that hydrolysis is an important process in the metabolic fate of some of these compounds.[8]

A 3-alkoxy group gives compounds (XXII–XXVII) with high potency. Conversion *in vivo* into 3-hydroxybenzodiazepines seems much less likely than is the case with the 3-acyloxy compounds. In two compounds (XXVIII and XXIX) bearing substituted alkoxy groups, potency is low. The 3-chloro compounds (XXX–XXXII) resemble the 3-alkoxy compounds in potency.

Sulfur-containing substituents result in lowered potency in relation to their oxy analogs (XXXIII *vs.* I, XXXIV *vs.* VII). The effect of amino substituents is dependent upon the nature of the amine, but only XXXVII and XXXVIII have high potency. Acylation of 3-amines reduces activity (XLIV and XLV *vs.* XXXVII). A 3-carbethoxy substituent results in an effective compound (LIII).

In three examples (LIV–LVI) in which two functional groups are placed in the 3 position, potency remains high only in LIV. Two compounds (XI and XLII) illustrate the harmful effect upon potency of a 3-methyl substituent added to an existing 3 substituent.

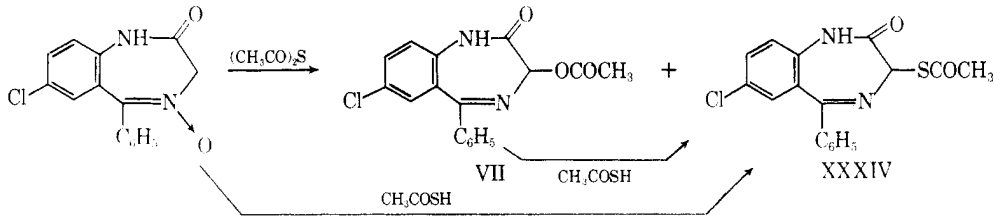
Experimental Section

The capillary melting points were determined in an oil bath and are not corrected. Compounds whose elemental analyses are indicated only by symbols showed values within 0.4% of the theoretical values.

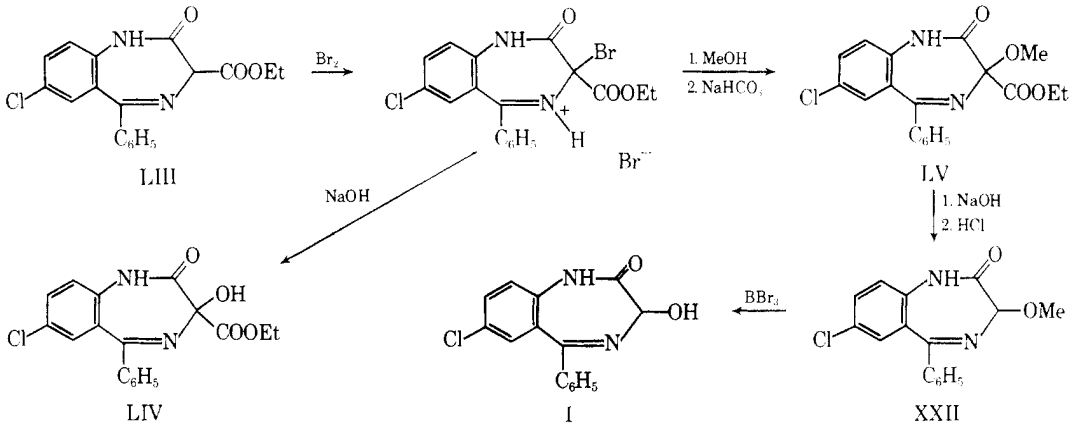
3-Acetoxy-7-chloro-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (XI).—To a suspension of 4.0 g of 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide[3] in 40 ml of AcOH was added with stirring 20 ml of Ac_2O. The solution was heated on the steam bath for 15 min and concentrated *in vacuo*. Recrystallization of the residue from ethanol gave 1.8 g of XI.

(8) S. S. Walkenstein, R. Wiser, C. H. Gudmundsen, H. B. Kimmel, and R. A. Corradino, *J. Pharm. Sci.*, **53**, 1181 (1964).

SCHEME II



SCHEME III



7-Chloro-3-diethylamino-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (XLII).—Compound XI (1.3 g) was dissolved in 25 ml of Et_2NH and allowed to stand at room temperature for 1 hr. The solvent was removed *in vacuo* and the residue was recrystallized twice from EtOH giving 0.6 g of XLII.

2-Acetyl-6-chloro-4-phenylquinazoline.—To a suspension of 2 g of XI in EtOH was added a slight excess of 6 *N* HCl with stirring. A complete solution resulted. The solvent was removed *in vacuo* and the residue was recrystallized several times from EtOH affording 0.35 g of product, mp 132–134°. *Anal.* ($C_{16}H_{11}ClN_2O$) C, H, N, Cl.

7-Chloro-1,3-dihydro-5-phenyl-3-succinoxy-2H-1,4-benzodiazepin-2-one (XVII).—To 75 ml of pyridine was added with stirring a mixture of 37 g of I and 37 g of succinic anhydride. In a few minutes the reaction mixture solidified. After heating on the steam bath for 80 min, the reaction mixture was cooled and diluted with 50 ml of EtOH. Addition of H_2O precipitated 57 g of XVII pyridinium salt, mp 139–141°. Recrystallization from EtOAc did not change the melting point. *Anal.* ($C_{24}H_{20}ClN_3O_5$) N.

A solution of 15 g of the pyridinium salt was dissolved in 200 ml of 50% EtOH and acidified with HCl. There was obtained 13.2 g of solid, mp 102–104°. Recrystallization from 50% EtOH–H_2O gave 9.8 g of XVII hydrate, mp 110–112°.

To 57 g of the pyridinium salt suspended in 1 l. of EtOH was added dropwise with stirring 1 equiv of 10% NaOH in 50% aqueous EtOH. During this time the starting compound dissolved and then the sodium salt precipitated out. Recrystallization from EtOH–H_2O gave 42 g of the hydrated sodium salt of XVII.

3-Acetoxy-1-chloroacetyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XXI).—A mixture of 3 g of VII and 10 g of chloroacetic anhydride was heated on the steam bath for several hours. After the reaction mixture became cool, AcOH was added, and 1.6 g of product was obtained which was recrystallized from a mixture of EtOAc and hexane.

Ethyl (7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yloxy)acetate (XXVIII).—Compound I (5 g) was gradually added to 55 ml of $SOCl_2$ and the mixture was heated at reflux for 1 hr. Excess $SOCl_2$ was evaporated on a rotary evaporator and trace quantities were removed by codistillation with toluene. The residue (XXX) was warmed on a steam bath with 16.2 g of ethyl glycolate until the solid dissolved (10–20 min). Upon standing for 2 days the oil partially crystallized and was filtered affording 2.9 g of crude product, mp 140–144°. Recrystallization from MeCN gave 1.6 g of XXVIII.

(7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yloxy)acetic Acid (XXIX).—Compound XXVIII (1.55 g) was dissolved in 15 ml of EtOH and 10 ml of 0.8 *N* NaOH and the solution was warmed on a steam bath for 10 min. The alcohol was removed on a rotary evaporator and the remaining yellow solution was diluted with 20 ml of H_2O and treated dropwise with stirring with 9 ml of 1.2 *N* HCl. The crude precipitate (mp 110–112°) was recrystallized from MeCN to afford 1 g of XXIX, mp 120°, then resolidified and melted at 205–207°.

7-Chloro-1,3-dihydro-3-mercapto-5-phenyl-2H-1,4-benzodiazepin-2-one (XXXIII).—To a stirred slurry of 1.4 g of XXXIV in 30 ml of EtOH was added 1.8 ml of 4 *N* NaOH. The white solid which separated after 5 min was dissolved by addition of 10 ml of H_2O and the solution was stirred an additional 5 min. The addition of 3 ml of AcOH diluted in 10 ml of H_2O caused the separation of 1.3 g of crystalline product, mp 138–139°. Recrystallization from EtOH afforded an analytical sample of XXXIII, hemiethanolate.

3-Acetylthio-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XXXIV).—7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (7.5 g) in 35 g of thioacetic acid was treated with 7.6 g of acetyl sulfide and the mixture was heated on the steam bath for 30 min. Evaporation of the excess reagents *in vacuo* afforded an oil which crystallized spontaneously upon treatment with EtOH to give 5.1 g of product, mp 205–206°. Recrystallization from EtOH gave an analytical sample of XXXIV, mp 208–209°.

In the absence of thioacetic acid a 4:6 (determined by nmr comparison of CH_3CO_2 absorptions) solid mixture of VII and XXXIV was obtained. Fractional crystallization of the solid mixture from EtOH afforded VII, mp 240–242°. The ir spectrum of the product was identical with that of an authentic sample of VII.

In the absence of thioacetic anhydride, a solution of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide in thioacetic acid heated for 2 hr on the steam bath afforded a small quantity of XXXIV.

Compound XXXIV from VII.—Compound VII (1.1 g) was heated in 5 g of thioacetic acid on a steam bath for 50 min. The excess thioacetic acid was evaporated *in vacuo* leaving an oily residue. Treatment of the residue with EtOH afforded 0.7 g of XXXIV, mp 206–208°. The ir spectrum of the product was identical with that of XXXIV.

7-Chloro-3-(2-diethylaminoethylthio)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XXXV).—To a mixture of 12.7 g of diethylaminoethanethiol hydrochloride and 10.0 g of Et_3N

in C_6H_6 was gradually added with stirring and cooling 7.6 g of XXX. After stirring for 3 hr, the reaction mixture was filtered from impurities, washed (H_2O), and concentrated *in vacuo*. To the residue was added petroleum ether (bp 30–60°) and 5.1 g of free base was collected and converted in C_6H_6 to the hydrochloride salt. Recrystallization from EtOH gave XXXV·HCl.

7-Chloro-1,3-dihydro-5-phenyl-3-(2-thiazolin-2-ylthio)-2H-1,4-benzodiazepin-2-one (XXXVI).—To a stirred suspension of 6.1 g of XXX and 3.5 g of 2-mercaptothiazoline in 50 ml of dioxane was added 3 g of Et_3N with cooling. The solution was stirred at room temperature for 1 hr. After filtration, the solution was concentrated at reduced pressure. The residue was washed (Et_2O, Me_2CO) and recrystallized from DMF to afford XXXVI.

7-Chloro-1,3-dihydro-3-(2-dimethylaminoethylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one (XLI).—Crude XXX was prepared from 5 g of I as in the preparation of XXVIII and dissolved in 50 ml of dimethoxyethane. The solution was added with stirring to a mixture of 10 ml of 2-dimethylaminoethylamine in 150 ml of 1,2-dimethoxyethane. After 20 min, the solvent was removed *in vacuo* and the residue was washed (H_2O) and recrystallized from EtOH giving 2.7 g of XLI.

7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-ylpyridinium Chloride (XLIII).—A mixture of 3 g of XXX, 1.1 g of pyridine, and 100 ml of acetone was heated under reflux for 1 hr. After the solution was cooled, 1.3 g of white solid was collected and recrystallized from MeCN to give XLIII.

Ethyl 7-Chloro-1-(ethoxycarbonyl)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carbamate (LII).—To a solution of 2 g of XXXVII·HCl in 35 ml of pyridine was added dropwise 4 ml of ethyl chloroformate. After stirring for 25 min the mixture was chilled and diluted with H_2O. LII (2.2 g) was collected and recrystallized from MeCN.

Ethyl 7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylate (LIII).—2-Amino-5-chlorobenzophenone (44 g) and 20 g of diethyl aminomalonate hydrochloride in 140 ml of pyridine were heated in an oil bath (150°) for 1 hr. An additional 30 g of diethyl aminomalonate hydrochloride in 60 ml of pyridine was added in three portions at 0.5-hr intervals. A constant volume of solvent was maintained by distillation of pyridine from the reaction mixture during the addition period. After a total reaction time of 4.75 hr, the pyridine was removed *in vacuo* and the viscous residue was taken up in benzene and washed (three times) with H_2O. The solution was dried (Mg_2SO_4) and concentrated *in vacuo* to a viscous oil. Treatment of the oil with 140 ml of MeCN gave 8.6 g of LIII. The ester was recrystallized from MeCN before analysis.

Ethyl 7-Chloro-2,3-dihydro-3-hydroxy-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylate (LIV).—Compound LIII (5 g) in 200 ml of CH_2Cl_2 was treated gradually with 2.8 g of Br_2 in 50 ml of CH_2Cl_2. The solution was treated with 75 mg of dibenzoyl peroxide and stirred at 27° for 16 hr. The solvent and excess Br_2 were removed *in vacuo* and the residue was dissolved in 50 ml of 1,2-dimethoxyethane and 20 ml of H_2O. The mixture was adjusted to pH 8 with 4 *N* NaOH and stirred for 35 min at 27°. The volatile solvents were removed *in vacuo* and the mixture was treated with 17 ml of 4 *N* NaOH thereby causing 5.7 g of a yellow solid to separate. The solid was dissolved in aqueous EtOH, the solution was filtered from impurities, and the filtrate was acidified with HCl to precipitate 1.6 g of product, mp 174–178°. Recrystallization from MeCN gave LIV.

Ethyl 7-Chloro-2,3-dihydro-3-methoxy-2-oxo-1H-1,4-benzodiazepine-3-carboxylate (LV).—Compound LIII (2 g) dissolved in 100 ml of CH_2Cl_2 was treated with a solution of 1.1 g of Br_2 in 5 ml of CH_2Cl_2. The mixture was stirred with 50 mg of dibenzoyl peroxide for 16 hr at 26°, treated with 2 ml of MeOH, and stirred for an additional 40 hr at 26°. The NH_4Br that separated was removed and the filtrate was evaporated *in vacuo* to an orange oil. Treatment of the oil with EtOAc caused 1.8 g of LV·HBr to separate, mp 190–191° dec. This salt was slurried in $CHCl_3$ and washed with $NaHCO_3$ solution. The $CHCl_3$ layer was dried (Mg_2SO_4) and evaporated *in vacuo* to an oil that crystallized on treatment with aqueous EtOH to give 1.3 g of product, mp 167–168°. Recrystallization from aqueous EtOH afforded an analytical sample of LV.

7-Chloro-1,3-dihydro-3-methoxy-5-phenyl-2H-1,4-benzodiazepin-2-one (XXII). A.—Compound LV (200 mg) dissolved in 6 ml of 1,2-dimethoxyethane and 6 ml of H_2O containing 0.8 ml of 4 *N* was heated at 95° for 16 hr. The solution was allowed to cool to 40° and was treated with 0.54 ml of 6 *N* HCl. The oily residue that remained after evaporation of the solvent was dissolved in CH_2Cl_2, and the solution was washed with $NaHCO_3$ solution and water and dried by passage through cotton. Evaporation of the solvent gave an oily residue that crystallized spontaneously on treatment with MeCN to afford 12 mg of XXII, mp 251–253°. A mixture melting point was undepressed. The ir spectrum of the product was identical with that of the material obtained from reaction of XXX and MeOH.

B.—Compound I (10 g) was added in portions over 25 min to 50 ml of concentrated H_2SO_4. The yellow solution was added with stirring to 400 ml of an ice–water slurry whereupon 10.6 g of a salt separated, mp 130–131° dec. A 2-g portion of the salt was heated in 15 ml of MeOH for 20 min on the steam bath until the material dissolved. On cooling 1.2 g of product (mp 248–254°) separated from the solution. Recrystallization from MeCN gave XXII.